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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/822,186	03/20/97	RUEGER	D CRP-137

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EXAMINER	
ROMEO, D.	
ART UNIT	**PAPER NUMBER**
1647	33

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 08/822,186	Applicant(s) Rueger et al.
	Examiner David Romeo	Group Art Unit 1647

☒ Responsive to communication(s) filed on *7 Dec 2000*.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-9, 11-25, 31-33, 35, and 36* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-9, 11-25, 31-33, 35, and 36* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☒ Claims *1-9, 11-25, 31-33, 35, and 36* are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

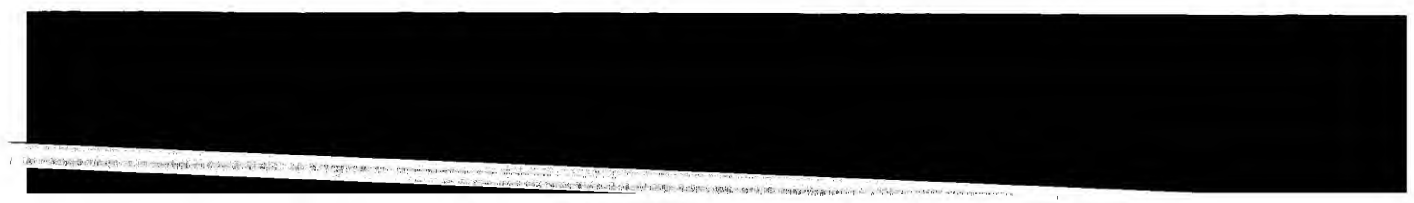
[redacted]

DETAILED ACTION

1. The request filed on 12/07/2000 (Paper No. 31) for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 08822186 is acceptable and a CPA has been established. An action on the CPA follows.

2. The preliminary amendment filed 12/07/2000 (Paper No. 32) has been entered. Claims 1-9, 11-33, 35 and 36 are pending. Claims 26-30 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b) as being drawn to a non-elected invention. Election was made **without** traverse in Paper No. 20. Applicant's elected without traverse OP-1, carboxymethyl cellulose, collagen, critical size defects in Paper No. 20. Claims 1-9, 11-25, 31-33, 35 and 36 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b) to the extent that they are drawn to a non-elected species. Election was made **without** traverse in Paper No. 20. Claims 1-9, 11-25, 31-33, 35 and 36 are being examined to the extent that they read upon OP-1, carboxymethyl cellulose, collagen, critical size defects.

3. Any objection and/or rejection of record that is not maintained and/or repeated in this Office action is withdrawn. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.



4. Claims 1-5, 7, 8, 9, 11, 12, 15, 16 are rejected under 35 U.S.C. 102(e) as being anticipated by Kuberasampath (aa9)[1]. Applicants argue that the examiner has misunderstood the claims and that the claims have been amended to exclude a matrix that is a synthetic polymer. Applicants' arguments have been fully considered but they are not persuasive. The instantly claimed device comprises a matrix, wherein the matrix does not comprise a synthetic polymer or demineralized bone. The transitional term "comprising", is inclusive or open-ended and does not exclude additional, unrecited elements. The term "comprising" leaves the claim open for the inclusion of unspecified ingredients even in major amounts. As such, the claimed device does not exclude a matrix that is a synthetic polymer. Kuberasampath's device comprises collagen (column 8, full paragraph 2). Collagen is a matrix, wherein the matrix does not comprise a synthetic polymer or demineralized bone, in accordance with claim 8 of the instant invention. Kuberasampath's device comprising collagen meets all the limitations of the claimed device. Furthermore, Kuberasampath teaches that the osteogenic protein may be produced using recombinant DNA techniques (column 3, lines 20-21). In accordance with Applicants' arguments, a recombinantly produced osteogenic protein is an "osteogenic protein being not associated with other osteogenic proteins with which it is normally associated".

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[1]Citations by the examiner are in an alphanumeric format, such as "(a1)", wherein the "a" refers to the reference cited on the Notice of References Cited, PTO-892, and the "1" refers to the Paper No. to which the Notice of References Cited, PTO-892, is attached.

5. Claims 1, 32, 33, 35 and 36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kuberasampath (aa9) as applied to claim 1 above. Applicants argue that the rejected claims do exclude the use of a synthetic polymer as a matrix. Applicants' arguments have been fully considered but they are not persuasive. The instantly claimed device comprises a matrix, wherein the matrix does not comprise a synthetic polymer or demineralized bone. The transitional term "comprising", is inclusive or open-ended and does not exclude additional, unrecited elements or method steps. The term "comprising" leaves the claim open for the inclusion of unspecified ingredients even in major amounts. As such, the claimed device does not exclude a matrix that is a synthetic polymer. Kuberasampath's device comprises collagen (column 8, full paragraph 2). Collagen is a matrix, wherein the matrix does not comprise a synthetic polymer or demineralized bone, in accordance with claim 8 of the instant invention. Kuberasampath's device comprising collagen meets all the limitations of the claimed device. Furthermore, Kuberasampath teaches that the osteogenic protein may be produced using recombinant DNA techniques (column 3, lines 20-21). In accordance with Applicants' arguments, a recombinantly produced osteogenic protein is an "osteogenic protein being not associated with other osteogenic proteins with which it is normally associated".

6. Claims 1, 13, 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kuberasampath (aa9) as applied to claim 1 above, and further in view of Wozney (BE, cited by

Applicants) and Amman (BA, cited by Applicants). Applicants argue that the rejected claims do exclude the use of a synthetic polymer as a matrix. Applicants' arguments have been fully considered but they are not persuasive. The instantly claimed device comprises a matrix, wherein the matrix does not comprise a synthetic polymer or demineralized bone. The transitional term "comprising", which is synonymous with "including," "containing," or "characterized by," is inclusive or open-ended and does not exclude additional, unrecited elements or method steps. The term "comprising" leaves the claim open for the inclusion of unspecified ingredients even in major amounts. As such, the claimed device does not exclude a matrix that is a synthetic polymer. Kuberasampath's device comprises collagen (column 8, full paragraph 2). Collagen is a matrix, wherein the matrix does not comprise a synthetic polymer or demineralized bone, in accordance with claim 8 of the instant invention. Kuberasampath's device comprising collagen meets all the limitations of the claimed device. Furthermore, Kuberasampath teaches that the osteogenic protein may be produced using recombinant DNA techniques (column 3, lines 20-21). In accordance with Applicants' arguments, a recombinantly produced osteogenic protein is an "osteogenic protein being not associated with other osteogenic proteins with which it is normally associated".

Applicants argue, citing Exhibit 1, that the prior art teaches away from the claimed combination. Applicants' arguments have been fully considered but they are not persuasive. In spite of the incompatibilities noted in Exhibit 1, the prior art of Tucker (a33) at the paragraph

bridging pages 6-7 teaches the combination of collagen and CMC in osteogenic devices. In spite of the incompatibilities noted in Exhibit 1, the prior art of Amman (BA, cited by Applicants) at page 10, lines 28-34, teaches the combination of collagen and CMC in osteogenic devices. In spite of the incompatibilities noted in Exhibit 1, the prior art of Kuberasampath (aa9) teaches mixtures of collagen and methycelluloses. The evidence of teaching away of Exhibit 1 does not outweigh the evidence of obviousness. It is further noted that a nexus between the incompatibilities noted in Exhibit 1, and their particular use in an osteogenic device has not been established, insofar as exhibit 1 does not say anything regarding osteogenic devices.

Applicants further urge that a synergistic effect at low doses does not mean that this advantage only exist at low doses. Applicants' arguments have been fully considered but they are not persuasive. Applicants have not shown that the unexpected properties at low doses have a significance equal to or greater than the expected properties of the claimed invention, which are not limited to low doses. The evidence of unexpected results is not sufficient to rebut the evidence of obviousness. Furthermore, the specification teaches that there were no marked differences in the histologic appearance between the standard OP1 sites and the standard dose OP1/CMC sites (page 86, lines 18-19).

Applicants further argue that there is no motivation to combine the references. Applicants' arguments have been fully considered but they are not persuasive. It is prima facie obvious to combine methods each of which is taught by the prior art to be useful for the same purpose, i.e.

osteogenesis. The idea or motivation to substitute CMC for methyl cellulose flows logically from each having been taught individually in the prior art for a common purpose, i.e. osteogenic devices. Each of Wozney and Amman teach that CMC and MC are useful for such purposes as the device of Kuberasampath was intended. Furthermore, Amman recognizes the equivalency of CMC and MC at page 16, full paragraph 1.

New formal matters, objections, and/or rejections:

Claim Rejections - 35 USC § 112

7. Claims 1, 17, 20, 23, 31 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Support for the limitation "not associated with other osteogenic proteins with which it is normally associated in vivo" cannot be found in the disclosure as originally filed and the introduction of such a limitation raises the issue of new matter. Applicants' arguments have been fully considered but they are not persuasive. Although recombinant osteogenic proteins can be "not associated with other osteogenic proteins with which it is normally associated in vivo", not all osteogenic proteins that are "not associated with other osteogenic proteins with which it is normally associated in vivo" are recombinant, such as osteogenic proteins from natural sources that are purified using conventional protein purification

techniques to the extent that they are "not associated with other osteogenic proteins with which it is normally associated in vivo". The scope of recombinant proteins is narrower than that of "not associated with other osteogenic proteins with which it is normally associated in vivo" and the introduction of the limitation "not associated with other osteogenic proteins with which it is normally associated in vivo" broadens the disclosure and raises the issue of new matter.

Claim Rejections - 35 USC § 102

8. Claims 1, 7-9, 11-14, 20-24 are rejected under 35 U.S.C. 102(b) as being anticipated by Amman (BA, cited by Applicants). Amman at page 10, lines 28-34, teaches the combination of collagen and CMC in osteogenic devices. The osteogenic device further comprises TCP (page 9, lines 12-16). Amman also teaches recombinant TGF-β1 (page 19, lines 29-30), which is an osteogenic protein. In accordance with Applicants' arguments, a recombinantly produced osteogenic protein is an "osteogenic protein being not associated with other osteogenic proteins with which it is normally associated". The combination of any of the polymers at page 10, lines 28-34, encompass a device comprising at least two different binding agents. Amman also teaches a device containing 0.1:1 to 1:1 amylopectin (binding agent):TCP(matrix) which encompasses one part binding agent and 5 parts matrix. Amman also teaches a device comprising zero parts binding agent (page 9, lines 12-16).

9. Claims 20, 22 are rejected under 35 U.S.C. 102(b) as being anticipated by Beck (CA, cited by Applicants). Beck teaches a composition comprising recombinant TGF-β1, and methycellulose (page 1257, column 2, full paragraph 1), which is a device comprising a purified osteogenic protein capable of inducing said repairs and a carrier, wherein said carrier comprises one part binding agent and zero parts matrix.

10. Claims 1-5, 7-9, 11-13, 31 are rejected under 35 U.S.C. 102(e) as being anticipated by Tucker (a33). Tucker teaches an osteogenic device comprising recombinant (column 3, line 24; column 6, lines 42-45) OP1 (column 4, lines 52-56; paragraph bridging columns 6-7), collagen and CMC (column 4, full paragraph 1; column 13, lines 45-57).

Claim Rejections - 35 USC § 103

11. Claims 1-5, 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Amman (BA, cited by Applicants) and Kuberasampath (aa9). Amman at page 10, lines 28-34, teaches the combination of collagen and CMC in osteogenic devices. The osteogenic device further comprises TCP (page 9, lines 12-16). Amman also teaches recombinant TGF-β1 (page 19, lines 29-30), which is an osteogenic protein. In accordance with Applicants' arguments, a recombinantly produced osteogenic protein is an "osteogenic protein being not associated with other osteogenic proteins with which it is normally associated". The combination of any of the

polymers at page 10, lines 28-34, encompass a device comprising at least two different binding agents. Amman also teaches a device containing 0.1:1 to 1:1 amylopectin (binding agent):TCP(matrix) which encompasses one part binding agent and 5 parts matrix. Amman also teaches a device comprising zero parts binding agent (page 9, lines 12-16). Amman also teaches BMPs (page 11, last paragraph). Amman does not teach recombinant OP1.

Kuberasampath teaches that the osteogenic protein OP1 may be produced using recombinant DNA techniques (column 3, lines 17-44). In accordance with Applicants' arguments, a recombinantly produced osteogenic protein is an "osteogenic protein being not associated with other osteogenic proteins with which it is normally associated". Kuberasampath does not teach an osteogenic device comprising TGF-β1. However, it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to make an osteogenic device comprising TGF-β1, as taught by Amman, and to modify that teaching by making an osteogenic device comprising OP1, as taught by Kuberasampath, with a reasonable expectation of success. One of ordinary skill in the art would be motivated to make this modification because Kuberasampath teaches that OP1 is useful for the purposes for which Amman is intended, namely bone induction.

Amman also teaches that the polysaccharide, wherein the polysaccharide is CMC, is generally present in a gel formulation in the range of 1-90% by weight of the gel (page 16, lines 5-7, and lines 10-13), which encompass at least approximately 180 mg of CMC per 1000 mg of collagen. One of ordinary skill in the art would be motivated to make an osteogenic device

comprising OP1, said OP1 not being associated with other osteogenic proteins with which it is normally associated in vivo, collagen and CMC, wherein the device contains 1-90% CMC by weight of the gel, with a reasonable expectation of success, because Amman teaches that polysaccharide generally present in a gel formulation in the range of 1-90% by weight of the gel is useful for making osteogenic devices.

The invention is prima facie obvious over the prior art.

12. Claims 1, 6, 15, 16, 32, 33, 35, 36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Amman (BA, cited by Applicants) and Ogawa (u4). Amman at page 10, lines 28-34, teaches the combination of collagen and CMC in osteogenic devices. The osteogenic device further comprises TCP (page 9, lines 12-16). Amman also teaches recombinant TGF-β1 (page 19, lines 29-30), which is an osteogenic protein. In accordance with Applicants' arguments, a recombinantly produced osteogenic protein is an "osteogenic protein being not associated with other osteogenic proteins with which it is normally associated". The combination of any of the polymers at page 10, lines 28-34, encompass a device comprising at least two different binding agents. Amman also teaches a device containing 0.1:1 to 1:1 amylopectin (binding agent):TCP(matrix) which encompasses one part binding agent and 5 parts matrix. Amman also teaches a device comprising zero parts binding agent (page 9, lines 12-16). Amman also teaches

BMPs (page 11, last paragraph). Amman does not teach an osteogenic device comprising two different osteogenic proteins.

Ogawa teaches that TGF-β and BMP synergize in promoting the formation of endochondral bone *in vivo* (page 14233, paragraph bridging columns 1-2). Ogawa does not teach an osteogenic device comprising TGF-β1, collagen and CMC. However, it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to make an osteogenic device comprising TGF-β1, collagen and CMC, as taught by Amman, and to modify that teaching by making an osteogenic device comprising TGF-β and BMP, as taught by Ogawa, with a reasonable expectation of success. One of ordinary skill in the art would be motivated to combine these teachings in order to achieve the synergistic effect of two different osteogenic proteins and induce more bone growth.

Amman is silent with respect to the presence of saline. Ogawa teaches wetting an osteogenic device with saline (page 14234, column 1, full paragraph 1). Ogawa does not teach wetting an osteogenic device comprising TGF-β1, collagen and CMC with saline. However, it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to make an osteogenic device comprising TGF-β1, collagen and CMC, as taught by Amman, and to modify that teaching by wetting the device with saline, as taught by Ogawa, with a reasonable expectation of success. One of ordinary skill in the art would be motivated to combine these teachings in order to mold the osteogenic device into a shape suitable for implantation.

Amman and Ogawa do not teach the kit of claims 32, 33, 35, 36. However, it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to provide pre-formulated matrix-osteogenic protein in a receptacle and provide the binding agent and wetting agent in separate receptacles with a reasonable expectation of success. One of ordinary skill in the art would be motivated to do this so that the osteogenic device could be formulated to the desired consistency.

Alternatively, it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to provide the matrix, osteogenic protein and binding agent in a single receptacle that had been pre-formulated for a pre-determined application with a reasonable expectation of success. One of ordinary skill in the art would be motivated to do so in order to prevent mistakes in the formulation of the device for a pre-determined application.

The invention is prima facie obvious over the prior art.

13. Claims 17-19, 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Amman (BA, cited by Applicants) and Cook (CD, cited by Applicants) in view of Ogawa (u4). Amman at page 10, lines 28-34, teaches the combination of collagen and CMC in osteogenic devices. The osteogenic device further comprises TCP (page 9, lines 12-16). Amman also teaches recombinant TGF-β1 (page 19, lines 29-30), which is an osteogenic protein. In accordance with Applicants' arguments, a recombinantly produced osteogenic protein is an "osteogenic protein being not

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associated with other osteogenic proteins with which it is normally associated". The combination of any of the polymers at page 10, lines 28-34, encompass a device comprising at least two different binding agents. Amman also teaches a device containing 0.1:1 to 1:1 amylopectin (binding agent):TCP(matrix) which encompasses one part binding agent and 5 parts matrix. Amman also teaches a device comprising zero parts binding agent (page 9, lines 12-16). Amman also teaches BMPs (page 11, last paragraph). Amman also teaches that the polysaccharide, wherein the polysaccharide is CMC, is generally present in a gel formulation in the range of 1-90% by weight of the gel (page 16, lines 5-7, and lines 10-13), which encompass at least approximately 200 mg of CMC per 1000 mg of collagen. Amman does not teach at least approximately 2.5 mg of OP1 per 1000 mg of collagen.

Cook discloses a composite of bovine bone collagen and rhOP-1 (page 303, column 2, full paragraph 1). The composite had the consistency of wet sand, which was spooned into the segmental defect site (paragraph bridging pages 303-304). Cook also teaches 2.5 mg of OP1 mixed with 500 mg of collagen (page 303, column 2, full paragraph 1), which is equal to at least approximately 2.5 mg of OP1 per 1000 mg of collagen, as recited in claim 19. Cook also teaches recombinant hOP1 (page 303, column 2, full paragraph 1), which is OP1 not being associated with other osteogenic proteins with which it is normally associated in vivo. Cook does not teach an osteogenic device comprising OP1, said OP1 not being associated with other osteogenic proteins with which it is normally associated in vivo, collagen and CMC wherein the device

[redacted]

contains at least approximately 200 mg of CMC per 1000 mg of collagen. However, it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to make an osteogenic device comprising TGF-β1, said TGF-β1 not being associated with other osteogenic proteins with which it is normally associated in vivo, collagen and CMC wherein the device contains at least approximately 200 mg of CMC per 1000 mg of collagen, as taught by Amman, and to modify that teaching by using 2.5 mg of OP1 per 500 mg of collagen, as taught by Cook, with a reasonable expectation of success. One of ordinary skill in the art would be motivated to make this modification because 2.5 mg of OP1 per 500 mg of collagen is useful for making osteogenic devices. Amman and Cook are silent with respect to the presence of saline.

Ogawa teaches wetting an osteogenic device with saline (page 14234, column 1, full paragraph 1). Ogawa does not teach wetting an osteogenic device comprising OP1, collagen and CMC with saline. However, it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to make an osteogenic device comprising OP1, collagen and CMC, as taught by Amman and Cook, and to modify that teaching by wetting the device with saline, as taught by Ogawa, with a reasonable expectation of success. One of ordinary skill in the art would be motivated to combine these teachings in order to mold the osteogenic device in to a shape suitable for implantation. The invention is prima facie obvious over the prior art.

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Conclusion

14. No claims are allowable.

ANY INQUIRY CONCERNING THIS COMMUNICATION OR EARLIER COMMUNICATIONS FROM THE EXAMINER SHOULD BE DIRECTED TO DAVID S. ROMEO WHOSE TELEPHONE NUMBER IS (703) 305-4050. THE EXAMINER CAN NORMALLY BE REACHED ON MONDAY THROUGH FRIDAY FROM 6:45 A.M. TO 3:15 P.M.

IF ATTEMPTS TO REACH THE EXAMINER BY TELEPHONE ARE UNSUCCESSFUL, THE EXAMINER'S SUPERVISOR, GARY KUNZ, CAN BE REACHED ON (703) 308-4623.

OFFICIAL PAPERS FILED BY FAX SHOULD BE DIRECTED TO (703) 308-4242.

FAXED DRAFT OR INFORMAL COMMUNICATIONS SHOULD BE DIRECTED TO THE EXAMINER AT (703) 308-0294.

ANY INQUIRY OF A GENERAL NATURE OR RELATING TO THE STATUS OF THIS APPLICATION OR PROCEEDING SHOULD BE DIRECTED TO THE GROUP RECEPTIONIST WHOSE TELEPHONE NUMBER IS (703) 308-0196.

David Romeo

DAVID ROMEO
PRIMARY EXAMINER
ART UNIT 1647

FEBRUARY 25, 2001

[redacted]